(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00275 A1

(51) International Patent Classification[7]: A61L 31/14, 31/04, 31/10, 27/56, 27/14, 27/34

(21) International Application Number: PCT/GB01/02786

(22) International Filing Date: 22 June 2001 (22.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0015430.2 24 June 2000 (24.06.2000) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/00275 A1

(54) Title: BIO-COMPATIBLE POLYMERIC MATERIALS

(57) Abstract: A method of making a medical device or part thereof includes a step of forming a porous layer on the outside of a support material, wherein the porous layer is, in preferred embodiments, selected from polyetherketone and polyetheretherketone. The porous layer may be prepared in a method which includes treating a region on the outside of a support material to render it porous and such treatment may involve diffusing a supercritical fluid into the polymer to render it porous or using a solvent to dissolve polymer at the surface, followed by subsequent precipitation at the surface. Alternatively, a material which is arranged to be porous may be applied to the support material wherein such a porous material may be a foam. In a further alternative, a material may be rendered porous after it has been contacted with the support material for example by virtue of it comprising a removable material for example a salt. Medical devices and methods of making such devices are also described.

BIO-COMPATIBLE POLYMERIC MATERIALS

This invention relates to bio-compatible polymeric materials and particularly, although not exclusively, relates to a method of making a medical device, for example a prosthesis or part thereof using such a material and such a device per se.

Much research is being directed to the provision of materials to meet the growing need for prosthetic devices such as orthopaedic, dental or maxillofacial implants. For example, nearly half a million patients receive bone implants each year in the US with the majority being artificial hip and knee joints made from titanium or colbalt-chrome alloys. However, these materials are too stiff leading to bone resorption, loosening of the implant and, consequently, have lifetimes of less than 10 years. Additionally, medical devices or prostheses such as pacemakers, vascular grafts, stents, heart valves, catheters and dental implants that contact body tissues or fluids of living persons or animals have been developed and used clinically.

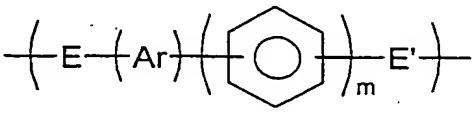
A major problem with medical devices such as those described is the susceptibility to foreign body reaction and possible rejection. Consequently, it is of great interest to the medical industry to develop materials from which medical devices can be made which are less prone to adverse biological reactions that typically accompany introduction of medical devices into humans or animals.

Furthermore, it is preferred that bio-compatible materials do not exist passively when introduced into

human or animal bodies but become integrated, for example osseo-integrated therewith. However, it is an ongoing problem to produce materials which have optimum physical (e.g. strength, modulus, wear resistance) and chemical (e.g. chemical stability, bio-stability, bio-compatibility) properties which are readily integratable with human or animal body tissues.

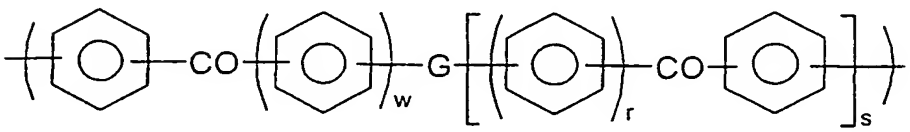
It is an object of the present invention to address the abovedescribed problems.

According to a first aspect of the present invention, there is provided a method of making a medical device or part thereof, the method including the step of forming a porous layer on the outside of a support material, wherein said porous layer includes a polymer having a moiety of formula



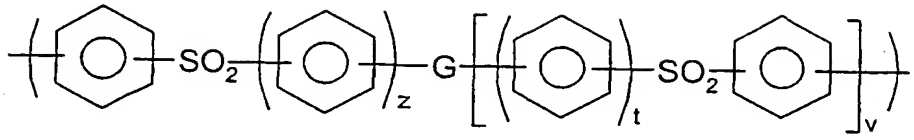
I

and/or a moiety of formula



II

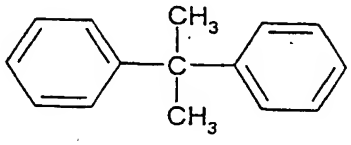
and/or a moiety of formula



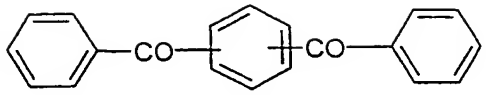
III

wherein the phenyl moieties in units I, II, and III are independently optionally substituted and optionally cross-linked; and wherein m,r,s,t,v,w and z independently represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following moieties (i)*, (i)**, (i) to (x) which is bonded via one or more of its phenyl moieties to adjacent moieties

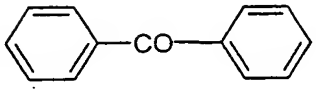
(i)**



(i)*



(i)



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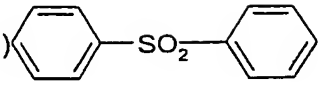
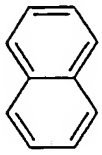


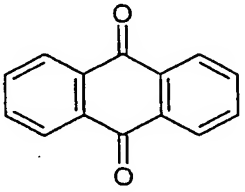
(iii)

(iv)

(v)



(vi)



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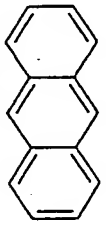

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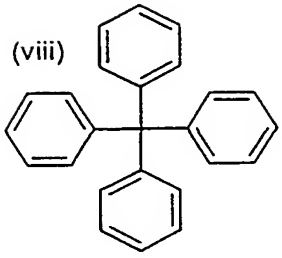

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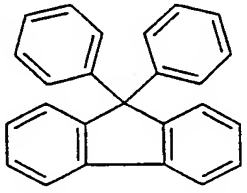
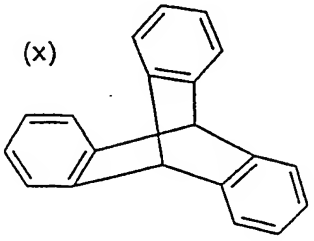


(x)



The invention extends to a method of making a medical device or part thereof, the method including the step of forming a porous layer on the outside of the support material from a polymer having moieties I, II and/or III as described.

Except where otherwise stated, throughout this specification, any alkyl, akenyl or alkynyl moiety suitably has up to 8, preferably up to 6, more preferably up to 4, especially up to 2, carbon atoms and may be of

straight chain or, where possible, of branched chain structure. Generally, methyl and ethyl are preferred alkyl groups and C_2 alkenyl and alkynyl groups are preferred.

Except where otherwise stated in this specification, optional substituents of an alkyl group may include halogen atoms, for example fluorine, chlorine, bromine and iodine atoms, and nitro, cyano, alkoxy, hydroxy, amino, alkylamino, sulphinyl, alkylsulphinyl, sulphonyl, alkylsulphonyl, amido, alkylamido, alkoxycarbonyl, haloalkoxycarbonyl and haloalkyl groups. Preferably, optionally substituted alkyl groups are unsubstituted.

Said porous layer preferably includes pores (hereinafter "surface pores") which open at the surface of said porous layer thereby to enable tissues to grow into the pores to aid integration of said medical device and/or part when introduced into a human or animal body. Suitably, surface pores have a diameter of at least 10μm, preferably at least 25μm, more preferably at least 50μ, especially at least 100μm, although it should be appreciated that a surface may include pores having diameters which are larger or smaller than those mentioned.

Suitably, the average diameter of said surface pores is at least 10μm, preferably at least 25μm, more preferably at least 50μm, especially at least 100μm. In some cases, the average diameter may be greater than 200μm or even greater than 300μm. The average diameter may be less than 600μm, suitably less than 500μm, preferably less than 400μm, more preferably less than 300μm, especially less than 200μm.

The diameter may be measured using a low magnification optical microscope with scale in visual frame.

Said porous layer preferably includes a majority of pores of at least 10μm, preferably at least 25μm, more preferably at least 50μm, especially at least 100μm.

In the context of this specification, a "majority" may mean at least 50%, suitably greater than 65%, preferably greater than 80%, more preferably greater then 95%, especially greater than 98%.

Said porous layer may have a density of at least 400 $mg.cm^{-3}$, preferably at least 500 $mg.cm^{-3}$, more preferably at least 600 $mg.cm^{-3}$. Said density may be 1000 $mg.cm^{-3}$ or less.

Said porous layer may have an average porosity of at least 20%, suitably at least 30%, preferably at least 40%, more preferably at least 50%. The porosity may be less than 90%, suitably less than 80%, preferably less than 70%. In some cases, the porosity may be less than 60%. Porosity may be measured by any suitable technique, for example by mercury intrusion porosimetry.

Said porous layer preferably includes pore interconnections having average diameters of at least 50μm, for example as measured using mercury intrusion porosimetry.

Said porous layer preferably includes a three-dimensional network of interconnected pores. Three-dimensional networks as described rarely connect through

straight channels. Preferably, said porous layer includes a network of interconnected pores throughout its volume with substantially no straight paths therein longer than the diameter of the largest pore.

Said porous layer preferably has a thickness of at least 100μm, more preferably at least 250μm, especially at least 500μm. The thickness may be 10mm or less, preferably 5mm or less.

Unless otherwise stated in this specification, a phenyl moiety may have 1,4- or 1,3-, especially 1,4-, linkages to moieties to which it is bonded.

Said polymer may include more than one different type of repeat unit of formula I; more than one different type of repeat unit of formula II; and more than one different type of repeat unit of formula III. Preferably, however, only one type of repeat unit of formula I, II and/or III is provided.

Said moieties I, II and III are suitably repeat units. In the polymer, units I, II and/or III are suitably bonded to one another - that is, with no other atoms or groups being bonded between units I, II, and III.

Where the phenyl moieties in units I, II or III are optionally substituted, they may be optionally substituted by one or more halogen, especially fluorine and chlorine, atoms or alkyl, cycloalkyl or phenyl groups. Preferred alkyl groups are C_{1-10}, especially C_{1-4}, alkyl groups. Preferred cycloalkyl groups include cyclohexyl and multicyclic groups, for example adamantyl.

Another group of optional substituents of the phenyl moieties in units I, II or III include alkyls, halogens, C_yF_{2y+1} where y is an integer greater than zero, O-R^q (where R^q is selected from the group consisting of alkyls, perfluoralkyls and aryls), $CF=CF_2$, CN, NO_2 and OH. Trifluormethylated phenyl moieties may be preferred in some circumstances. Sulphonate moieties may also be preferred in some circumstances.

Preferably, said phenyl moieties are not optionally-substituted prior to formation of said porous layer. If, however, they are substituted, they are preferably substituted by moieties that can withstand injection moulding of the polymer. Phenyl moieties may be optionally-substituted (especially sulphonated) after formation of said layer as hereinafter described.

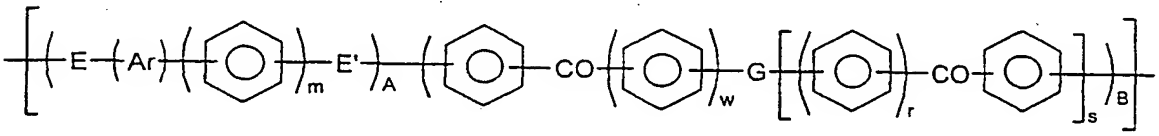
Where said polymer is cross-linked, it is suitably cross-linked so as to improve its properties. Any suitable means may be used to effect cross-linking. For example, where E represents a sulphur atom, cross-linking between polymer chains may be effected via sulphur atoms on respective chains. Preferably, said polymer is not optionally cross-linked as described.

Where w and/or z is/are greater than zero, the respective phenylene moieties may independently have 1,4- or 1,3-linkages to the other moieties in the repeat units of formulae II and/or III. Preferably, said phenylene moieties have 1,4- linkages.

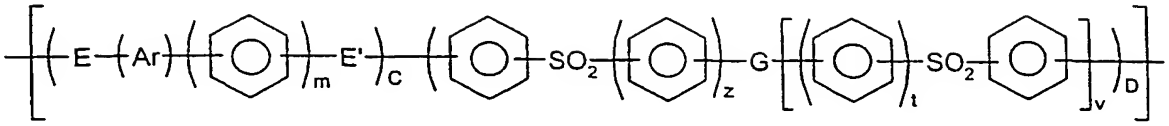
Preferably, the polymeric chain of the polymer does not include a -S- moiety. Preferably, G represents a direct link.

Suitably, "a" represents the mole % of units of formula I in said polymer, suitably wherein each unit I is the same; "b" represents the mole % of units of formula II in said polymer, suitably wherein each unit II is the same; and "c" represents the mole % of units of formula III in said polymer, suitably wherein each unit III is the same. Preferably, a is in the range 45-100, more preferably in the range 45-55, especially in the range 48-52. Preferably, the sum of b and c is in the range 0-55, more preferably in the range 45-55, especially in the range 48-52. Preferably, the ratio of a to the sum of b and c is in the range 0.9 to 1.1 and, more preferably, is about 1. Suitably, the sum of a, b and c is at least 90, preferably at least 95, more preferably at least 99, especially about 100. Preferably, said polymer consists essentially of moieties I, II and/or III.

Said polymer may be a homopolymer having a repeat unit of general formula



or a homopolymer having a repeat unit of general formula

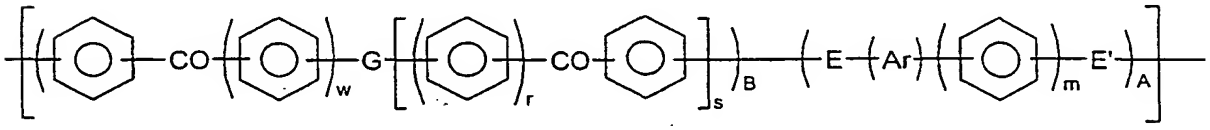


V

or a random or block copolymer of at least two different units of IV and/or V

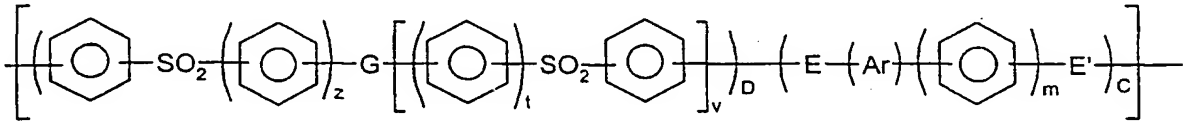
wherein A, B, C and D independently represent 0 or 1 and E,E',G,Ar,m,r,s,t,v,w and z are as described in any statement herein.

As an alternative to a polymer comprising units IV and/or V discussed above, said polymer may be a homopolymer having a repeat unit of general formula



IV*

or a homopolymer having a repeat unit of general formula



V*

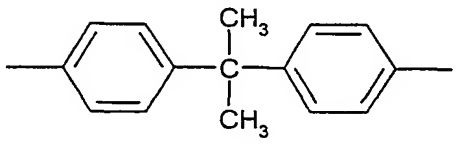
or a random or block copolymer of at least two different units of IV* and/or V*, wherein A, B, C, and D independently represent 0 or 1 and E, E', G, Ar, m, r, s, t, v, w and z are as described in any statement herein.

Preferably, m is in the range 0-3, more preferably 0-2, especially 0-1. Preferably, r is in the range 0-3, more preferably 0-2, especially 0-1. Preferably t is in the

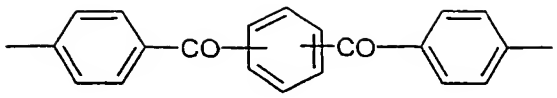
range 0-3, more preferably 0-2, especially 0-1. Preferably, s is 0 or 1. Preferably v is 0 or 1. Preferably, w is 0 or 1. Preferably z is 0 or 1.

Preferably, said polymer is a homopolymer having a repeat unit of general formula IV.

Preferably Ar is selected from the following moieties (xi)*, (xi)**,(xi) to (xxi):

(xi)** 

(xi)*



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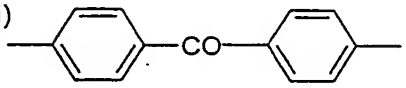
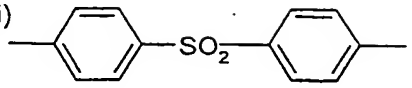
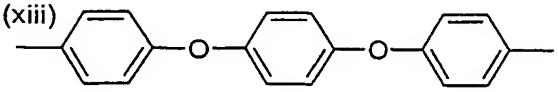


(xii)



(xiii)



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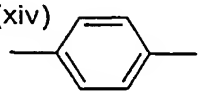
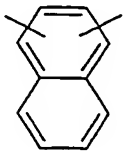


(xv)



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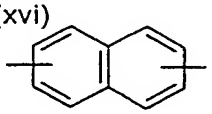
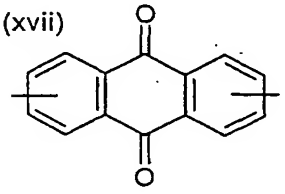
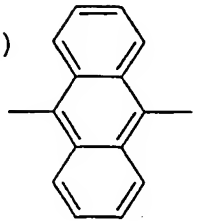


(xvii)



(xviii)



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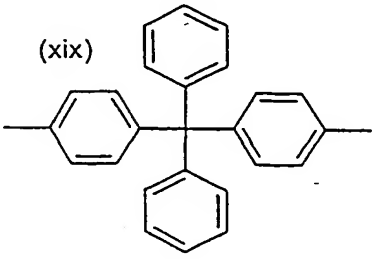

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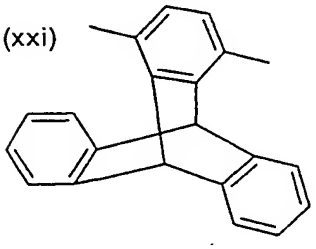

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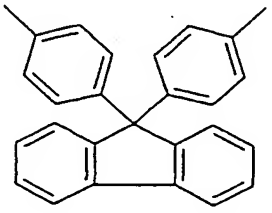


In (xi)*, the middle phenyl may be 1,4- or 1,3-substituted.

Preferably, (xv) is selected from a 1,2-, 1,3-, or a 1,5- moiety; (xvi) is selected from a 1,6-, 2,3-, 2,6- or a 2,7- moiety; and (xvii) is selected from a 1,2-, 1,4-, 1,5-, 1,8- or a 2,6- moiety.

One preferred class of polymers does not include any moieties of formula III, but suitably only includes moieties of formulae I and/or II. Where said polymer is a homopolymer or random or block copolymer as described, said homopolymer or copolymer suitably includes a repeat unit of general formula IV. Such a polymer may, in some embodiments, not include any repeat unit of general formula V.

Suitable moieties Ar are moieties (i)*, (i), (ii), (iii) and (iv) and, of these, moieties (i)*, (i) and (iv) are preferred. Other preferred moieties Ar are moieties (xi)*, (xii), (xi), (xiii) and (xiv) and, of these, moieties (xi)*, (xi) and (xiv) are especially preferred.

An especially preferred class of polymers are polymers which consist essentially of phenyl moieties in conjunction with ketone and/or ether moieties. That is, in the preferred class, the polymer does not include repeat units which include -S-, $-SO_2-$ or aromatic groups other than phenyl. Preferred polymers of the type described include:

(a) a polymer consisting essentially of units of formula IV wherein Ar represents moiety (iv), E and E' represent oxygen atoms, m represents 0, w represents 1, G represents a direct link, s represents 0, and A and B represent 1 (i.e. polyetheretherketone).

(b) a polymer consisting essentially of units of formula IV wherein E represents an oxygen atom, E' represents a direct link, Ar represents a moiety of structure (i), m represents 0, A represents 1, B represents 0 (i.e. polyetherketone);

(c) a polymer consisting essentially of units of formula IV wherein E represents an oxygen atom, Ar represents moiety (i)*, m represents 0, E' represents a direct link, A represents 1, B represents 0, (i.e. polyetherketoneketone).

(d) a polymer consisting essentially of units of formula IV wherein Ar represents moiety (i), E and E' represent oxygen atoms, G represents a direct link, m represents 0, w represents 1, r represents 0, s represents 1 and A and B represent 1. (i.e.polyetherketoneetherketoneketone).

(e) a polymer consisting essentially of units of formula IV, wherein Ar represents moiety (iv), E and E' represents oxygen atoms, G represents a direct link, m represents 0, w represents 0, s, r, A and B represent 1 (i.e. polyetheretherketoneketone).

Of the aforesaid, the polymers described in (a) and (b) are preferred, with the polymer described in (a) being especially preferred.

The glass transition temperature (T_g) of said polymer may be at least 135°C, suitably at least 150°C, preferably

at least 154°C, more preferably at least 160°C, especially at least 164°C. In some cases, the Tg may be at least 170°C, or at least 190°C or greater than 250°C or even 300°C.

Said polymer may have an inherent viscosity (IV) of at least 0.1, suitably at least 0.3, preferably at least 0.4, more preferably at least 0.6, especially at least 0.7 (which corresponds to a reduced viscosity (RV) of least 0.8) wherein RV is measured at 25°C on a solution of the polymer in concentrated sulphuric acid of density 1.84gcm^{-3}, said solution containing 1g of polymer per 100cm^{-3} of solution. IV is measured at 25°C on a solution of polymer in concentrated sulphuric acid of density 1.84gcm^{3}, said solution containing 0.1g of polymer per 100cm^{3} of solution.

The measurements of both RV and IV both suitably employ a viscometer having a solvent flow time of approximately 2 minutes.

The main peak of the melting endotherm (Tm) for said polymer (if crystalline) may be at least 300°C.

Preferably, said polymer has at least some crystallinity or is crystallisable. The existence and/or extent of crystallinity in a polymer is preferably measured by wide angle X-ray diffraction, for example as described by Blundell and Osborn (Polymer 24, 953, 1983). Alternatively, crystallinity may be assessed by Differential Scanning Calorimetry (DSC).

Said polymer may have a number average molecular weight in the range 2000-80000. Preferably said molecular weight

is at least 14,000. The molecular weight may be less than 60,000.

Said porous layer may include one or more fillers for providing desired properties. Said porous layer preferably incorporates an X-ray contrast medium. Fillers and/or said X-ray contrast medium is/are preferably distributed substantially uniformly throughout said porous layer.

Where an X-ray contrast medium is provided it suitably comprises less than 25wt%, preferably less than 20wt%, more preferably less than 15wt%, especially less than 10wt% of said porous layer. Where it is provided, at least 2wt% may be included. Preferred X-ray contrast mediums are particulate and preferably are inorganic. They preferably have low solubility in body fluids. They preferably also have a sufficient density compared to that of the polymeric material to create an image if a compounded mixture of the polymer and contrast medium are X-ray imaged. Barium sulphate and zirconium oxide are examples of X-ray contrast media. Said particulate material is suitably physically held in position by entrapment within the porous layer.

It has been found that the pore size and density of a said porous layer can be a function of the X-ray contrast medium and/or other fillers present. For example, at 20% filler level, the resultant pores are predominantly in the range 30 to 60 μm, whereas at 10% filler level, the pores are predominantly in the range 70 to 120μm.

Said support material may be made out of any suitable material for example a metal or plastics material. Preferably, however, said support material comprises a

polymer which preferably includes a moiety of formula I and/or a moiety of formula II and/or a moiety of formula III as described above. Said polymer of the support material may have any feature of the polymer in said porous layer except, preferably, said support material has lower porosity compared to the porous layer and preferably is substantially non-porous. Said support material and said porous layer may include the same material or a different material, but preferably both materials include phenyl moieties, carbonyl and/or sulphone moieties, and ether or thio-ether moieties, in the polymer backbone.

Whilst said support material preferably includes moieties I, II and/or III and the preferred polymers which include moieties I, II and III described above with reference to the porous layer are preferred for said support material, phenyl groups of said moieties are preferably not optionally-substituted or cross-linked. Preferably, said support material comprises any of the polymers described in paragraphs (a) to (e) above and, of these, the polymers in (a) and (b) are preferred with the polymer in (a) being especially preferred.

Said support material preferably comprises a major amount of said polymer. Where said support material comprises more than one polymer having moieties I, II and/or III the sum of the amounts of respective said polymers preferably represents a major amount.

In the context of this specification, a "major" amount may mean greater than 50wt%, suitably greater than 65wt%, preferably greater than 80wt%, more preferably greater than 95wt%, especially greater than 98wt% of the

referenced material is present relative to the total weight of relevant material present.

Said support material preferably comprises a unitary arrangement. That is, it preferably does not comprise a series of layers of material or include areas thereof having a higher concentration of one component compared to another. Said support material preferably has a thickness in at least one region thereof of at least 5mm, preferably at least 10mm, more preferably at least 20mm. Said support material preferably does not consist of a coating (or the like) on another material which provide a support for the device or part thereof.

Said support material suitably has a tensile strength (according to ISO R527) of at least 80, preferably at least 90, especially at least 95 MPa. The tensile strength may be less than 360, suitably less than 250, preferably less than 140 MPa. It preferably has an elongate at break (according to ISO R527) of at least 40, preferably at least 50%. It preferably has a tensile modulus (according to ISO R527) of greater than 2.5, preferably greater than 3, especially greater than 3.5 GPa. The tensile modulus may be less than 40, suitably less than 30, preferably less than 20, more preferably less than 10 GPa. It preferably has a flexural strength (according to ASTM D695) of at least 100, more preferably at least 110, especially at least 115 MPa. The flexural strength may be less than 650, preferably less than 400, more preferably less than 260, especially less than 200 MPa. It preferably has a flexural modulus (according to ISO R178) of at least 3, preferably at least 3.5, especially at least 4 GPa. The flexural modulus may be

less than 60, suitably less than 25, preferably less than 20, especially less than 10 GPa. Advantageously, the aforementioned properties can be adjusted by appropriate selection of polymers and/or any reinforcement means included in said support material to suit particular applications. For example, a continuous carbon fibre polyetheretherketone may typically have a tensile strength of about 350 MPa, a tensile modulus of 36 GPa, an elongation of 2%, a flexural modulus of 50 GPa and a flexural strength of 620 MPa. A polyaryetherketone with 30% of high performance fibres may typically have a tensile strength of 224 MPa, a tensile modulus of 13 GPa, a tensile elongation of 2%, a flexural modulus of 20 GPa and a flexural strength of 250 MPa.

A said porous layer may be provided on any part of said medical device or part thereof which may come into contact with body fluids in use.

The method of the first aspect may include a first method type which includes treating a region on the outside of said support material to render it porous. The region which is treated may be a part of said support material (in which case it suitably includes a polymer having moieties I, II and/or III described herein) or may comprise a layer of a polymer having moieties I, II and/or III which is applied to the support material (which preferably comprises a polymer having moieties I, II and/or III) prior to the treatment. Thus, said layer which is to be rendered porous is preferably part of or associated with said support material prior to said layer being rendered porous. Preferably, said layer which is to be rendered porous comprises a polymer having moieties I,

II and/or III, wherein phenyl moieties in moieties I, II and/or III are not optionally-substituted or optionally cross-linked. Said layer which is to be rendered porous optionally includes an X-ray contrast medium as described therein.

Preferably, said support material is arranged in a shape which represents or is a precursor of a medical device or part thereof. Optionally, a said layer of polymer may be applied to said support material. A said region of said layer may then be rendered porous.

In a first embodiment of said first method type, said support material having at least a layer of a said polymer having moieties I, II and/or III is placed in an environment which is at a temperature of at least 20°C above the glass transition temperature of the polymer and at least 30°C below the melting temperature of the polymer. The environment is suitably pressurised, suitably at 20-50 MPa, with a supercritical fluid, especially carbon dioxide. Consequently, the fluid diffuses into the polymer. After a suitable dwell time, the fluid pressure may be released and preferably the temperature in the environment is reduced, suitably relatively rapidly, below the glass transition temperature of the polymer. The layer on the outside of the support material is thereafter found to be porous.

Advantageously, by adjusting the temperature, fluid pressure and/or time in the environment, the properties and/or arrangement of the porous layer formed can be varied to suit any particular application and/or desired characteristics.

Preferably, in the first embodiment of the first method type, the polymer rendered porous may not be functionalised in the method and, accordingly, the polymer prior to and subsequent to the treatment is chemically unchanged.

In a specific example of said first embodiment of said first method type, a useful porous layer may be formed using supercritical carbon dioxide at 260°C and 34.5 MPa (5,000 psig) for 4.5 hours.

In a second embodiment of said first method type, a surface of said support material having at least a layer of said polymer having moieties I, II and/or III is contacted with a solvent in order to dissolve polymer at said surface. To this end, said support material may be immersed in the solvent. After a time, the polymer is caused to precipitate at the surface by diluting the solvent, for example by contacting said surface with a solvent which is not capable of solvating the polymer. The depth of the porous layer and/or pore sizes are dependent upon the nature of the solvent, the solvent concentration, the temperature and the time of contact of said solvent with said support material. Examples of suitable solvents that may be used to dissolve include sulphuric acid, methanesulphonic acid and phenol/dichlorobenzene.

Some solvents may, in addition to solvating the polymer, chemically react with it to functionalise it. Sulphonating solvents, for example sulphuric acid such as 98% sulphuric acid, may sulphonate polymers of the type

described. For example, said solvent may sulphonate phenyl moieties in $-O-(Ph)_n-O-$ moieties in said polymer where Ph represents a phenyl moiety and n represents an integer (preferably 1). Thus, in some cases, a porous functionalised (e.g. sulphonated) layer may be produced in the method. Thus, in this case, the polymer rendered porous may be chemically changed during the treatment, for example by functionalisation of phenyl moieties as described.

The method of the first aspect may include a second method type wherein a layer of material which is arranged to be porous (hereinafter "precursor material") is applied to the support material, wherein said precursor material includes a polymer having moieties I, II and/or III as described herein. Said precursor material suitably includes at least 30wt%, preferably at least 40wt%, more preferably at least 50wt%, especially at least 60wt% of a said polymer having moieties I, II and/or III. Said precursor material may include an X-ray contrast medium as described. Any desired depth of said precursor material may be applied to the support according to the desired depth of the porous layer.

In a first embodiment of said second method type, said precursor material is applied as a porous material. For example, a foamed material may be applied to the support material. Supercritical carbon dioxide may be used as described with reference to said first embodiment of said first method. Thus, said polymer having moieties I, II and/or III and any other components which are to make up the precursor material may be heated in an environment at a temperature of at least 20°C above the glass transition

temperature of the polymer used and at least 30°C below the melting temperature of the polymer. The environment is suitably pressurised with a supercritical fluid, especially carbon dioxide so that the fluid diffuses into the polymer. The molten mixture may be extruded into an atmosphere of lower pressure, whereupon as the pressure on the melt reduces upon exiting an extrusion orifice, a foam is formed. This foam may be injection moulded on to the support material or, alternatively, the molten mixture and the support material may be co-extruded so that the foam is directly transferred to the support material as it exits an extruder.

In the first embodiment of the second method type, said polymer of said precursor material is not chemically changed, for example functionalised in the method and, accordingly, said polymer before and after contact with said support material is chemically unchanged.

In a second embodiment of the second method type, said precursor material is arranged to be rendered porous, suitably after it has been contacted with the support material. To this end, preferably, said precursor material comprises a material (hereinafter a "removable material") which can be removed, for example dissolved out of said precursor material, when said precursor material is present on the support material, whereby a porous structure is produced by virtue of the voids defined in regions from which said removable material has been removed. Thus, the method preferably includes contacting the precursor material, when it is present on said support material, with solvent which solubilises the removable material but not the polymer having moieties I, II and/or

III. Preferably, the polymer is semi-crystalline so as to render it less soluble in solvents that may be used to solubilise the removable material.

In said second embodiment of the second method type, said polymer of said precursor material is not functionalised in the method, so said polymer before and after contact with said solvent is preferably chemically unchanged.

In a first example of said second embodiment of said second method type, said removable material may comprise an amorphous high temperature polymer or polymers which is/are preferably blended with said polymer having moieties I, II and/or III, wherein each amorphous polymer used is incompatible with said polymer having moieties I, II and/or III. Blending is preferably by a melt process, suitably using a twin screw extruder. The total amount of said amorphous polymer in the blend may be less than 40%wt. An X-ray contrast medium may be included in the blend as described herein. After blending, the blend may be contacted with the support material for example by being injection moulded or extruded directly onto the support material. After solidification of the blend, the morphology is that of a continuous matrix of the larger volume component (e.g, the polymer having moieties I, II and/or III) with domains of the lower volume component (e.g. the removable material) or a bi-continuous network of different materials.

The method may then involve immersing the composite comprising support material and precursor material in a solvent which will dissolve out the removable material

leaving a microporous structure of the polymer having moieties I, II and/or III that is firmly attached to the support. The solvent may be selected to effect dissolution according to the identity of the removable material.

The identity and/or physical form of the amorphous polymer affects the nature of the porous layer produced in the method. Whilst polysulphone or polyethersulphones may be used, there is a tendency for the resultant pores produced to be too small for bone ingrowth. It is preferred that polymers are selected which, when removed, yield pores, preferably a majority thereof, in the range 50-500μm. Suitable polymers may be less compatible with said polymer having moieties I, II and/or III (especially the preferred examples thereof described herein) than polyethersulphone or polysulphone is with said polymer. Said removable material is preferably a polymer which does not include ether groups in its polymer chain. If said removable material has a polymer backbone of the same type as described for said polymer having moieties I, II and/or III, there are preferably bulky groups pendent from the backbone to render it incompatible with said polymer having moieties I, II and/or III. It is especially preferred for said removable material not to be a polyketone or polysulphone polymer. Examples of preferred polymers are high temperature nylons, high temperature silane polymers and polymers that incorporate fluorine atoms.

In a second example of said second embodiment of said second method type, said removable material may comprise a fugitive compound which is preferably blended with said

polymer having moieties I, II and/or III. Said fugitive compound is preferably thermally stable at 400°C and preferably includes particles, preferably a majority thereof, in the range 50-500μm. At least 5wt%, preferably at least 20wt%, more preferably at least 15wt% of said fugitive compound may be present in the precursor material. The amount of said compound in said precursor material is preferably less than 60wt%, more preferably less than 50wt%, especially 40wt% or less. Said precursor material may include an X-ray contrast medium, as described, for example in the range 3-25wt%.

Preferred fugitive compounds are inorganic, especially inorganic salts. A carbonate, especially calcium carbonate, is especially preferred.

Preferably, the polymer having moieties I, II and/or III is filled with said fugitive compound and said X-ray contrast medium, if provided, using a melt processing technique. The blend may be contacted with the support material for example by being injection moulded or extruded directly onto the support material. After solidification, the composite of support material and precursor material is immersed in a solvent to remove the fugitive compound and yield a microporous three-dimensional surface. The solvent used is preferably an acid, for example hydrochloric acid. Advantageously, the acid used has a negligible effect on the polymer having moieties I, II and/or III itself.

In a further embodiment, a porous material may be prepared as described in applicant's co-pending application no GB 0101098.2. The method described therein

may be used to prepare a porous (foamed) layer on the outside of a support material. The layer may be formed by heating a mixture which includes a said polymer having moieties I, II and/or III and a decomposable material comprising a magnesium moiety and a hydroxide moiety (e.g. magnesium hydroxide) to a foaming temperature at or above the decomposition temperature of the decomposable material. The porous layer may be extruded onto the support material.

In any of the embodiments described, the method may include a further treatment of a porous layer after it has been formed, for example to reveal elements of the microporous structure that would otherwise not be exposed to body fluids, in use. Further treatment may involve machining the porous layer after it has been prepared. Furthermore, in some embodiments, the method may involve removing the porous layer in its entirety, for example in regions of the medical device or part thereof that do not contact body fluids in use or otherwise are not required to be adapted for bone ingrowth in osseo-integration.

The method of the first aspect may include associating bio-compatible moieties with said polymer which includes moieties I, II and/or III of said porous layer.

The method preferably includes the step of treating said polymer with a material for providing bio-compatible moieties (hereinafter "BCM material"). Said BCM material may be arranged to provide any of the bio-compatible moieties described hereinafter. Said polymer may be provided as a solid. Suitably, said bio-compatible moieties are caused to become associated with a surface of

said porous layer of said solid. Said solid is preferably shaped so as to represent at least a part of a device for use in medical applications, as described above. Preferably, after association with said bio-compatible moieties, the bio-compatible material formed (referred to as "bio-compatible polymeric material") is not engineered or otherwise treated in a manner which may result in substantial depletion of the bio-compatible moieties associated with its surface.

In the scientific literature there is inconsistency in the use of descriptions such as "bio-compatible", "bio-active" and "bio-materials". In the context of the present specification, the term "bio-compatible" has generally been used to refer to a material which is compatible with use in medical applications, for example by not being toxic or otherwise harmful to living materials. It also encompasses materials which have a biological or physiological effect when associated with living materials.

Preferably, said bio-compatible polymeric material has improved or enhanced bio-compatibility compared to said polymer having moieties I, II and/or III in said porous layer, in the absence of associated bio-compatible moieties.

Bio-compatible moieties suitably include moieties arranged to reduce adverse biological reactions when the bio-compatible polymeric material is introduced into (or otherwise associated with) a human or animal body. For example, adverse biological reactions associated with introduction into a human or animal body of said polymer

having said bio-compatible moieties may be less compared to use of the same polymer but which does not include associated bio-compatible moieties.

"Bio-compatible moieties" referred to herein suitably refer to moieties which are compatible with use in medical applications, for example by not being toxic or otherwise harmful to living material. Such bio-compatible moieties may be arranged to bond (for example to form ionic or covalent bonds) or otherwise interact with materials present in human or animal bodies in order to improve their integration and acceptance by such bodies.

A said bio-compatible moiety may be selected from an anticoagulant agent such as heparin and heparin sulfate, an antithrombotic agent, a clotting agent, a platelet agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defence agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein such as avidin, a glycoprotein, a globular protein, a structural protein, a membrane protein and a cell attachment protein, a peptide such as a glycopeptide, a structural peptide, a membrane peptide and a cell attachment peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent such as pencillin, ticarcillin, carbenicillin, ampicillin, oxacillian, cefazolin, bacitracin, cephalosporin, cephalothin, cefuroxime, cefoxitin, norfloxacin, perfloxacin and sulfadiazine, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, biotin, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a nucleotide, a polynucleotide, a

nucleoside, a lectin, a ligand and a dye (which acts as a biological ligand), a radioisotope, a chelated radioisotope, a chelated metal, a metal salt, a sulphonic acid or salt thereof, a steroid, a non-steroid, a non-steroidal anti-inflammatory, an analgesic, an anti-histamine, a receptor binding agent, a chemotherapeutic agent, a hydrophilic polymer (e.g. poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), ethylene oxide-propylene oxide block co-polymers, poly(N-vinyl-2-pyrrolidone) (PNVP), poly(2-hydroxyethyl methacrylate) (pHEMA), HEMA co-polymers, poly(vinyl alcohol) (PVA), polyacrylamide, its derivatives, poly(methyl methacrylate) (PMMA), suitably having a PEG chain on each of the side groups, polysiloxanes (e.g. polydimethylsiloxanes (PDMS)), ionic water-soluble polymers like poly(acrylic acid) (PAAc)) and a polyurethane. Examples of some of the aforesaid are provided in US5958430, US5925552, US5278063 and US5330911 and the contents of the aforementioned specifications are incorporated herein by reference.

In one embodiment, said bio-compatible moieties may comprise bone morphogenic protein (BMP) as described in US4563489 and patents cited therein and the contents of the aforesaid are incorporated herein. Said BMP may be provided in combination, for example in admixture, with a physiologically acceptable biodegradable organic polymer and said biodegradable polymer may be associated with said at least two moieties of said polymer of said bio-compatible polymeric material, for example by being covalently bonded to said at least two moieties. Thus, in this case, the combination of said biodegradable polymer and BMP defines said bio-compatible moieties. Said biodegradable polymer is preferably a biodegradable

polylactic acid; or alternatively, other physiologically acceptable biodegradable organic polymers which are structurally equivalent to polylactic acid can be used as the delivery system for BMP. Examples include poly(hydroxy organic carboxylic acids) e.g. poly(hydroxy aliphatic carboxylic acids), polyglycollic acid, polyglactin, polyglactic acid and poly adonic acids.

In another embodiment, said bio-compatible moieties may be selected from inorganic crystalline structures, inorganic amorphous structures, organic crystalline structures and organic amorphous structures. Preferred bio-compatible moieties are phosphorous based ceramics, for example calcium-phosphorous ceramics. Phosphates in general are suitable but calcium phosphates and calcium apatite are preferred. Especially preferred is hydroxyapatite, a synthetic Ca-P ceramic.

Whilst said bio-compatible moieties may be associated by any suitable means with the porous layer, for example by covalent bond(s), hydrogen bond(s), encapsulation in a matrix which is bonded to or otherwise interacts with said layer or by ionic interaction(s), it is preferred that there are covalent bonds between the bio-compatible moieties and said polymer having moieties I, II and/or III in said porous layer or there are ionic interactions between said bio-compatible moieties and said polymer.

The method may include functionalising said porous layer after its formation thereby to enable association with said bio-compatible moieties. Alternatively, said polymer which includes moieties I, II and/or III may be functionalised prior to or during formation of said porous

layer. An example of the latter is Example 2 hereinafter wherein the polymer is sulphonated during formation of said porous layer.

In one embodiment, wherein the porous layer includes hydroxy groups, the porous layer may be treated with a diisocyanate and a diol thereby to associate a polyurethane with said porous layer. Alternatively, wherein the porous layer includes isocyanate groups, the porous layer may be treated with a diisocyanate and a diol thereby to associate a polyurethane with said porous layer.

In the method of the first aspect, said support material is preferably formed into a shape which represents or is a precursor of a medical device or part thereof. Formation into a shape may use any suitable method, for example, moulding, machining of a blank, extrusion or the like. Then, said porous layer is formed on the outside of the support material in desired regions thereof using a method described herein. The porous layer may be further treated for example to functionalise it and/or to associate bio-compatible moieties with it.

Whilst the method may be used for making any type of medical device or part thereof (as described in the introduction of this specification) the medical device or part thereof is preferably for an orthopaedic implant, especially for a body joint, for example a hip or knee joint or spine fusion device.

The invention extends to a method of making a medical device or part thereof, the method comprising: forming a material into a shape which represents or is a precursor

of a device for use in medical applications wherein said material comprises a polymer; and treating material in said shape in order to define a porous layer on the outside of said shape, wherein said porous layer comprises a polymer having moieties I, II and/or III as described herein.

According to a second aspect of the invention, there is provided a medical device or part thereof which includes a support material and a porous layer on the outside of the support material, wherein said porous layer includes a polymer having a moiety of formula I and/or of formula II and/or of formula III as described according to the first aspect wherein said polymer is optionally associated with bio-compatible moieties.

Preferably, said support material also comprises a polymer having a moiety of formula I and/or II and/or III. Preferably, said polymer in the support material and said polymer in said porous layer have the same polymeric backbone. They may differ in terms of whether phenyl moieties are functionalised and/or since bio-compatible moieties may be associated with said porous layer. Preferably, the polymer is polyetheretherketone or polyetherketone or a functionalised derivative thereof

A polymer having a moiety of formula I and/or II and/or III may be prepared as described in PCT/GB99/02833.

The invention extends to a method of making a medical device or part thereof, the method including the step of forming a layer (hereinafter an "X-ray contrast layer") on

the outside of a support material, wherein said layer includes an X-ray contrast medium.

Said X-ray contrast layer may have any feature of the porous layer described herein. Said support material may have any feature of a said support material described in any statement herein. Preferably said support material includes a lower amount of X-ray contrast medium than said X-ray contrast layer. Preferably, said support material includes substantially no X-ray contrast medium.

Any feature of any aspect of any invention or embodiment described herein may be combined with any feature of any aspect of any other invention or embodiment described herein.

Specific embodiments of the invention will now be described, by way of example.

The following materials are referred to herein:

PEEK (Trade Mark) - polyetheretherketone obtained from Victrex Plc of England and/or prepared as described herein;

PEK (Trade Mark) - polyetherketone obtained from Victrex Plc and/or prepared as described herein.

Hydrofy GS 1.5 (Trade Mark) a mineral containing >90% magnesium hydroxide obtained from Nuova Sima Srl of Genga, Italy. It contains $Mg(OH)_2$ (92.5%), $MgCO_3$ (2.5%) $CaCO_3$ (4.2%), FeO_3 (0.5%) and Mn_3O_4 (0.01%) and has an average particle size of 1.8μm (by Sedigraph Micrometrics).

All chemicals referred to herein were used as received from Sigma-Aldrich Chemical Company, Dorset, U.K., unless otherwise stated.

Example 1 Preparation of a porous surface on PEK™ using concentrated sulphuric acid.

An injection moulded plaque of Victrex PEK™ (Melt Viscosity 0.22kNsm^{-2}, at 1000sec^{-1} at 400°C), 15cm x 15 cm x 3.2 mm was coated with a 100μm layer of 98% sulphuric acid at ambient temperature using a doctor blade. After 30 minutes the plaque was immersed in glacial acid at 5°C. After 1 hour the acid was replaced with deionised water. The plaque was washed in boiling water, followed by refluxing acetone then dried in oven at 50°C for 2 hours. The plaque had a porous surface of PEK™ with predominantly 50 - 400μm pores.

Example 2 Preparation of a porous surface on PEEK™ using concentrated sulphuric acid.

An injection moulded plaque of Victrex PEEK™ (Melt Viscosity 0.38kNsm^{-2}, at 1000sec^{-1} at 400°C), 15cm x 15 cm x 3.2 mm was coated with a 100μm layer of 98% sulphuric acid at ambient temperature using a doctor blade. After 30 minutes the plaque was immersed in glacial acid at 5°C. After 1 hour the acid was replaced with deionised water. The plaque was washed in boiling water, followed by refluxing acetone then dried in oven at 50°C for 2 hours. The plaque had a porous surface of sulphonated PEEK™ with predominantly 50 - 400μm pores.

Example 3 Formation of a porous surface on polyaryletheretherketone using calcium carbonate.

Polyaryletheretherketone 450G (Victrex plc) was mixed with nominally 250 μm particulate calcium carbonate at 40% by weight using a 25 mm single screw extruder. The resultant mixture was injection moulded into 3.2 mm thick plaques (150 x 150 mm). The plaques were transferred to a bath of 2M Hydrochloric acid. After a soak time of 2 hours the resultant plaque had a three dimensional micro-porous surface. The pores were measured in the range 60 to 300μm. It should be noted that due to the attrition experienced by the fugitive compound during the mixing phase in the extruder, the size of the resulting particles in the polymer were reduced from nominally 250μm to a range that yielded predominantly 60-300μm pores.

Example 4 Formation of foamed polyaryletherketone surfaces by supercritical CO_2

450G polyaryletheretherketone supplied by Victrex plc was mixed with nominally 100 micron barium sulphate powder (Merck, UK) in a Marion Tumble blender for 30 minutes. The resultant mixture was fed into a 32 mm single screw extruder. The mixture was extruded and cooled as a lace in air, prior to granulation. The mixed pellets were placed in trays (approximately 2.5 cm deep) in an air circulating oven at 130 °C for 5 hours. The pellets were then injection molded using a Neggri Bossi 100 tones clamping force moulder to form 150 mm x 150 mm x 6 mm plaques.

Plaques were then placed in a cavity 5 mm larger than the plaque depth and 10 mm wider than the plaque width and length. The cavity was placed in 200 tpsi heated platen press, fitted with thermocouples and a water cooling system. The nominal temperature of the platens was set to 280 C and the clamping force was increased to a maximum value. The temperature was allowed to stabilize prior to the cavity being pressurised with supercritical carbon dioxide at 40 MPa. The pressure and temperature was maintained for 5 hours.

After this time the pressure of the system was released and water cooling applied to the tool. The sample was removed from the tool when the thermocouple readings fell below 80 C. The plaque had the surface finish machined off (approximately 0.25 mm) to reveal a complex microstructure of pores. The pores were predominately in the size range 50 to 500 microns and discrete.

Example 5 Formation of extruded foamed polyaryletheretherketone using supercritical CO_2

High viscosity polyaryletheretherketone (450G) has been used in a series of experiments to produce foamed components of densities varying in the range 0.35 to 0.90 g cm^{-3}. The supercritical fluid used was CO_2 and was introduced to the melt after compaction via a poppet valve. After the introduction of the supercritical fluid the temperatures used to process the melt were reduced from 400 to 300 °C.

A preblended compound consisting of 5% by weight magnesium hydroxide (Hydrofy 1.5) and 450P polyetheretherketone supplied by Victrex plc was fed into an 1.5 inch Plaston single screw extruder and heated up in stages to approx 400°C. The extrudate was expelled through an adjustable slit die as a foam on to a strip of PEEK film cut to fit onto a laboratory sized band caster. As the bandcaster rotated the extruded material formed a drawn foamed layer on the surface of the PEEK film.

A section of this foamed composite strip was removed, mounted on a solid plaque and the foamed surface subjected to mechanical abrassion so as to revove the surface layer. The exposed surface structure was seen under an optical microscope as comprising a complex microstructure of pores. The pores were predominantly in the size range 50 to 200 microns.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

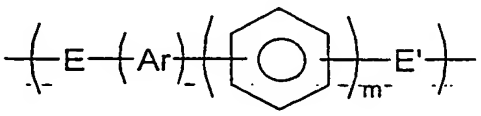
All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extend to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

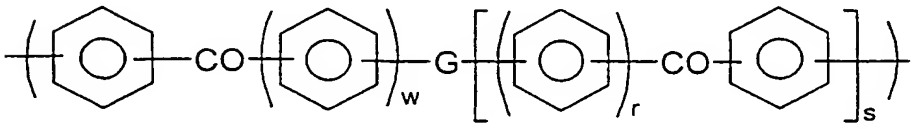
CLAIMS

1. A method of making a medical device or part thereof, the method including the step of forming a porous layer on the outside of a support material, wherein said porous layer includes a polymer having a moiety of formula



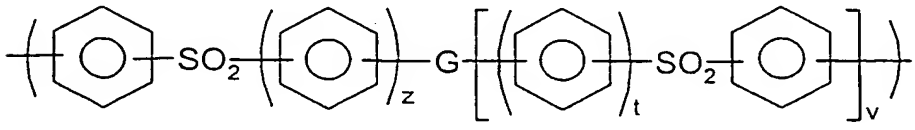
I

and/or a moiety of formula



II

and/or a moiety of formula

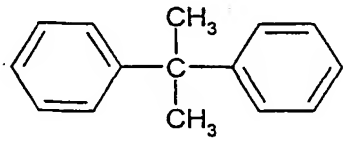


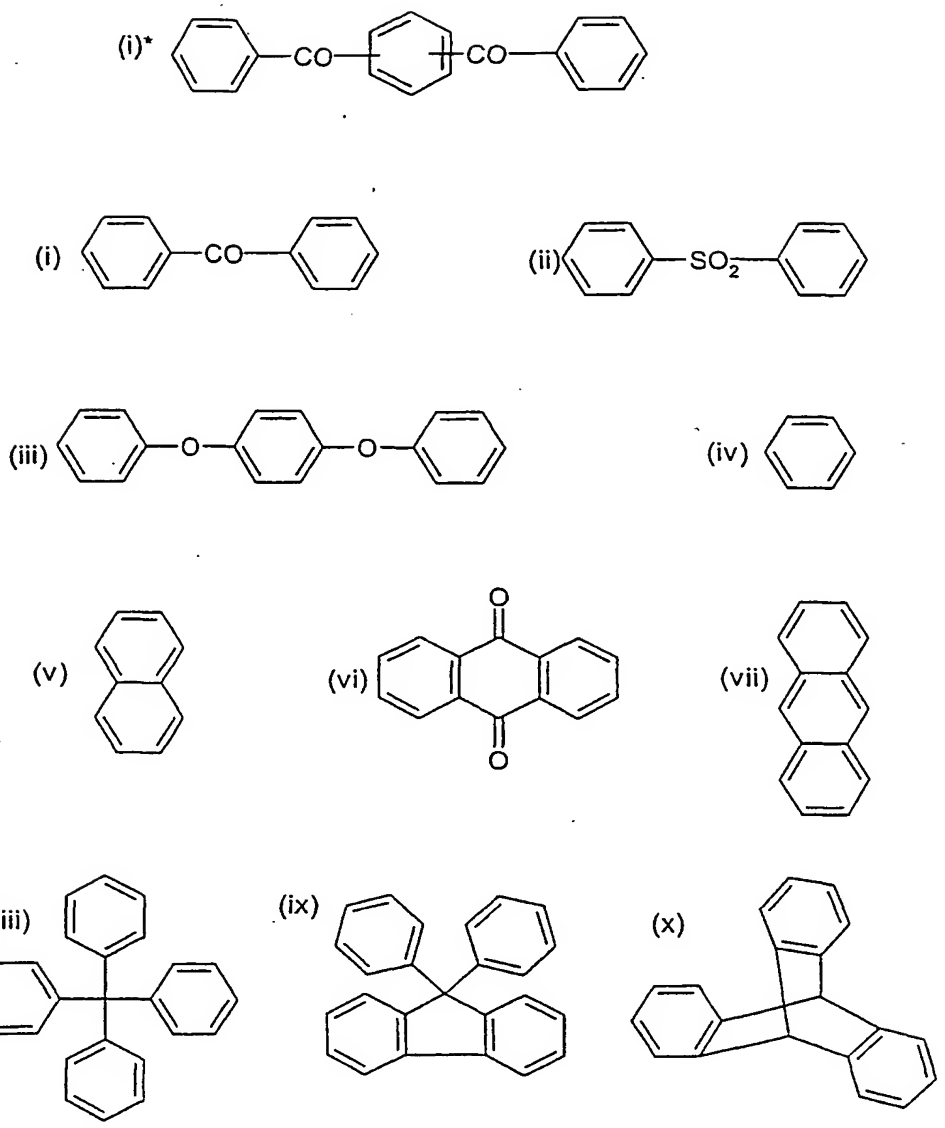
III

wherein the phenyl moieties in units I, II, and III are independently optionally substituted and optionally cross-linked; and wherein m,r,s,t,v,w and z independently

represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following moieties (i)*, (i)**, (i) to (x) which is bonded via one or more of its phenyl moieties to adjacent moieties

(i)**





2. A method according to claim 1, wherein said porous layer includes pores (hereinafter "surface pores") which open at the surface of the said porous layer thereby to enable tissues to grow into the pores to aid integration of said medical device and/or part when introduced into a human or animal body, wherein the average diameter of said surface pores is at least 10μm.

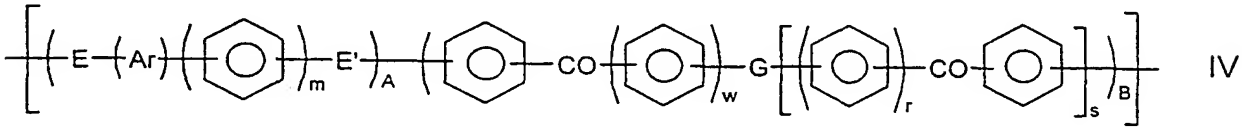
3. A method according to claim 2, wherein said average diameter is less than 600μm.

4. A method according to any preceding claim, wherein the porous layer has a density of at least 400mg.cm^{-3} and 1000mg.cm^{-3} or less.

5. A method according to any preceding claim, wherein said porous layer has an average porosity of at least 20% and less than 90%.

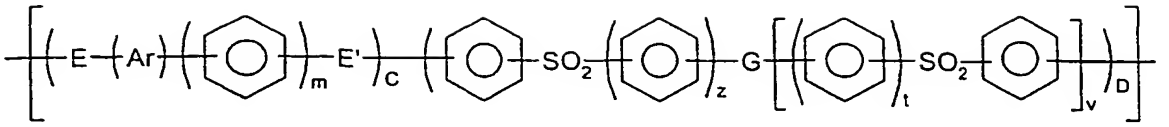
6. A method according to any preceding claim, wherein said porous layer has a thickness of at least 100μm and 10mm or less.

7. A method according to any preceding claim, wherein said polymer is a homopolymer having a repeat unit of general formula



IV

or a homopolymer having a repeat unit of general formula

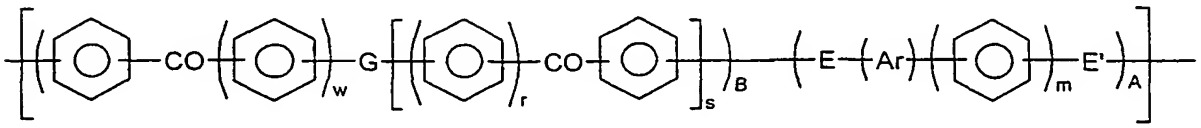


V

or a random or block copolymer of at least two different units of IV and/or V

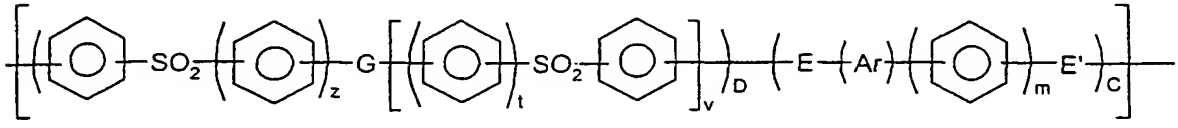
wherein A, B, C and D independently represent 0 or 1 and E,E',G,Ar,m,r,s,t,v,w and z are as described in claim 1; or

said polymer is a homopolymer having a repeat unit of general formula



IV*

or a homopolymer having a repeat unit of general formula



V*

or a random or block copolymer of at least two different units of IV* and/or V*, wherein A, B, C, and D independently represent 0 or 1 and E, E', G, Ar, m, r, s, t, v, w and z are as described in claim 1.

8. A method according to any preceding claim, wherein said polymer is selected from polyetheretherketone, polyetherketone, polyetherketoneketone,

polyetherketoneetherketoneketone and polyetheretherketoneketone.

9. A method according to any preceding claim, wherein said polymer is selected from polyetheretherketone and polyetherketone.

10. A method according to any preceding claim, wherein said polymer is polyetheretherketone.

11. A method according to any preceding claim, wherein said support material is made out of metal or a plastics material.

12. A method according to any preceding claim, wherein said support material comprises a polymer which includes a moiety of formula I and/or a moiety of formula II and/or a moiety of formula III as described in claim 1.

13. A method according to any preceding claim, wherein said support material and said porous layer include the same material or a different material provided, however, that both materials include phenyl moieties, carbonyl and/or sulphone moieties, and ether or thioether moieties, in the polymer backbone.

14. A method according to any preceding claim, the method including treating a region on the outside of said support material to render it porous.

15. A method according to claim 14, wherein said support material having at least a layer of a said polymer having moieties I, II and/or III is placed in an environment

which is at a temperature of at least 20°C above the glass transition temperature of the polymer and at least 30°C below the melting temperature of the polymer and said environment is pressurised with a supercritical fluid and thereafter the pressure is released.

16. A method according to claim 14, wherein a surface of said support material having at least a layer of a said polymer having moieties I, II and/or III is contacted with a solvent in order to dissolve polymer at said surface and, thereafter, the polymer is caused to precipitate at the surface by diluting the solvent.

17. A method according to claim 14, wherein a layer of material which is arranged to be porous (hereinafter "precursor material") is applied to the support material, wherein said precursor material includes a polymer having moieties I, II and/or III as described in claim 1.

18. A method according to claim 17, wherein said precursor material is applied as a porous material.

19. A method according to claim 17 or claim 18, wherein a foamed material is applied to the support material.

20. A method according to claim 17, wherein said precursor material is arranged to be rendered porous after it has been contacted with the support material and comprises a material (hereinafter a "removable material") which can be removed when said precursor material is present on the support material whereby a porous structure is produced by virtue of voids defined in regions from which said removable material has been removed.

21. A method according to claim 20, wherein said removable material comprises an amorphous high temperature polymer or polymers which is/are blended with said polymer having moieties I, II and/or III, wherein each amorphous polymer used is incompatible with said polymer having moieties I, II and/or III.

22. A method according to claim 20, wherein said removable material comprises a fugitive compound which is blended with said polymer having moieties I, II and/or III.

23. A method according to claim 17, wherein said layer is formed by heating a mixture which includes said polymer having moieties I, II and/or III and a decomposable material comprising a magnesium moiety and a hydroxide moiety to a foaming temperature at or above the decomposition temperature of the decomposable material.

24. A method according to any preceding claim which includes associating bio-compatible moieties with each polymer which includes moieties I, II and/or III of said porous layer.

25. A method of making a medical device or part thereof, the method comprising: forming a material into a shape which represents or is a precursor of a device for use in medical applications wherein said material comprises a polymer; and treating material in said shape in order to define a porous layer on the outside of said shape, wherein said porous layer comprises a polymer having moieties I, II and/or III as described in claim 1.

26. A medical device or part thereof which includes a support material and a porous layer on the outside of the support material, wherein said porous layer includes a polymer having a moiety of formula I and/or of formula II and/or of formula III as described in claim 1, wherein said polymer is optionally associated with bio-compatible moieties.

27. A medical device or part thereof according to claim 25, wherein said support material also comprises a polymer having a moiety of formula I and/or II and/or III.

28. A method of making a medical device or part thereof, the method including the step of forming a layer (hereinafter an "x-ray contrast layer") on the outside of a support material, wherein said layer includes an x-ray contrast medium.

INTERNATIONAL SEARCH REPORT

[redacted]national Application No
PCT/GB 01/02786

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/14 A61L31/04 A61L31/10 A61L27/56 A61L27/14
A61L27/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L C08G C08L C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, INSPEC, COMPENDEX, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 659 389 A (SCHNEIDER EUROP AG) 28 June 1995 (1995-06-28) abstract column 7, line 46 - line 58 column 8, line 19 - line 26	1-28
X	US 5 969 020 A (SHALABY SHALABY W ET AL) 19 October 1999 (1999-10-19) column 1, line 11 - line 27 column 4, line 23 - line 65 examples 11-13	1-28
X	EP 0 269 256 A (PFIZER HOSPITAL PROD) 1 June 1988 (1988-06-01) claims 1-14	1-28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" documen: which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2001	08/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muñoz, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]national Application No
PCT/GB 01/02786

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 4 859 715 A (DUBROW ROBERT S ET AL) 22 August 1989 (1989-08-22) abstract	1-28
X	RENARDY M ET AL: "MEMBRANES FOR A BIOHYBRID PANCREAS" ADVANCES IN BIOMATERIALS, 1990, pages 633-638, XP001034375 ISSN: 0272-3840 the whole document	1-28
P,X	EP 1 099 468 A (INST DEUTSCHE) 16 May 2001 (2001-05-16) the whole document	1-10, 14-19, 24-27
A	WO 91 09079 A (ERBA CARLO SPA) 27 June 1991 (1991-06-27) abstract	
A	EP 0 283 187 A (ICI PLC) 21 September 1988 (1988-09-21) column 2, line 6 - line 45 example 1	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27

   A method of making a medical device
   -forming a porous layer
   -the layer includes a polymer of formula I, II or III

2. Claim : 28

   a method of making a medical device
   -forming a layer
   -said layer includes an X-ray contrast medium

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7,11-28 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the polyetherketones such as those in claims 8-10.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

[redacted]national Application No
PCT/GB 01/02786

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